REMARKS

The present invention comprises methods and kits for the treatment of asthma and allergies. Claims 41, 45, 53, 54, 62, 64, 72, 73, 80, 81, 88 and 89 are presently under consideration. Claims 80-81 have been canceled and claim 64 has been amended herein.

Information Disclosure Statements (IDS)

Applicants acknowledge and appreciate the Examiner's consideration and return of an initialed copy of the IDS filed on June 22, 2000. Applicants also submitted a Supplementary IDS on September 26, 2002. However, an initialed copy of this document has not yet been returned. Applicants respectfully request consideration of the references cited in the Supplementary IDS and the return of an initialed copy of this Supplementary IDS to Applicants. A copy of this document is enclosed for the Examiner's convenience.

Objection to the Specification

The Examiner has indicated that the title of the invention is not descriptive and a new title is required. Applicants have amended the specification, particularly the title of the invention to read, "A Method of Treating Allergy By Administering An Anti-Histamine Antibody".

Objections to the Claims

The Examiner has objected to claims 53-54 and 80-81 under 37 C.F.R. §1.75 and MPEP §706.03(k). Specifically, in the Examiner's opinion, claims 53-54 are substantial duplicates of claims 80-81, respectively. While not necessarily agreeing with the Examiner, but rather in a good faith effort to expedite the prosecution of the present application, Applicants have canceled claims 80-81 herein without prejudice to their inclusion in any later filed divisional and continuation applications.

Rejection of claims 41, 62 and 88 under 35 U.S.C. §103(a)

The Examiner has rejected claims 41, 62 and 88 under 35 U.S.C. §103(a) as being unpatentable over Horsmanheimo et al. (1996, J. Allergy Clin. Immunol. 98: 408-411) in view of Wright et al. (1992, Critical Review in Immunology 12: 125-168). The Examiner contends that

Horsmanheimo et al. disclose an increased histamine release in the early allergic response, but fails to disclose administering antibodies to the histamine produced by an allergic response. The Examiner further contends that Wright et al. teach that administration of an antibody is effective immunotherapy because antibodies have structural and functional features that enhance their value in binding to antigens and can specifically block and inhibit antigens. The Examiner is of the opinion that it would have been *prima facie* obvious for one of skill in the art to use the antibodies taught by Wright et al. to inhibit and block the release of histamine with the expectation that the antibodies against histamine would be useful in treating allergy in a mammal and would be used for immunotherapy.

The three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these criteria have been met here.

Horsmanheimo et al. offer no suggestion or motivation to modify the reference or to combine their teachings with those of Wright et al. to arrive at the present invention. Horsmanheimo et al. teach that histamine and leukotriene C_4 (LTC_4) levels are increased in persons afflicted with mosquito bites, and that mosquito bites cause wheals and delayed bite papules. However, they also teach that cetirizine (sold under the brand name Zyrtec), an H_1 blocking antihistamine, decreases mosquito bite-induced wheal formation and pruritus significantly (page 408, second column). Thus, Horsmanheimo et al. teach that there is a treatment for the allergic response associated with mosquito bites, and it is not an anti-histamine antibody. In addition, Horsmanheimo et al. limit their teachings to mosquito bites, and there is no indication that the biological phenomena they report are characteristic of any allergy other than that induced by mosquito saliva. The skilled artisan, when equipped with the teachings of Horsmanheimo et al., would look no further than the four corners of the reference because

Horsmanheimo et al. teach that in their limited mosquito bite model, cetirizine is significantly effective, and one would not have to turn to Wright et al. in order to arrive at a method to treat the sequellae of a mosquito bite. Therefore, the skilled artisan would find no motivation in Horsmanheimo et al. in view of Wright et al. to arrive at the present invention.

Horsmanheimo et al. in view of Wright et al. similarly offer no reasonable expectation of success in arriving at the present invention. Horsmanheimo et al. teach that both histamine and LTC_4 are involved in the reaction to mosquito bites, but make no suggestion that histamine is the primary modulator of the allergic reaction. In fact, the data taught by Horsmanheimo et al. demonstrate that the LTC_4 reaction occurs in a greater proportion of the subjects than the histamine reaction (abstract, lines 7-11), that the LTC_4 levels increase by as much as 6 times whereas the histamine levels increase, at the very most, by a little more than 2-fold (Table 1, page 409), and that the LTC_4 levels rise later and persist longer (page 410, first column). Therefore, the data Horsmanheimo et al. disclose seems to indicate that LTC_4, and not histamine, is the more potent and effective modulator of mosquito bite reactions. Thus, the skilled artisan would have no reasonable expectation that antibodies to histamine would successfully alleviate the symptoms associated with a mosquito bite because the data disclosed by Horsmanheimo et al. indicate that LTC_4 may play a more crucial role.

Moreover, even though Horsmanheimo et al. indicate that LTC_4 is the prominent mediator of mosquito bite reactions, the role of histamine and LTC_4 in mosquito bites are taught in combination, and the skilled artisan, armed with Horsmanheimo et al, would have no reasonable expectation of success in administering anti-histamine antibodies without anti-LTC_4 antagonists. Therefore, the skilled artisan would have no reasonable expectation of success in arriving at the present invention.

Horsmanheimo et al. in view of Wright et al. similarly fail to teach or suggest all of the claims limitations. The present claims are directed to a method of treating an allergy, and are not limited to just mosquito bite reactions. There is no teaching in Horsmanheimo et al. that their findings are applicable to any conditions other than mosquito bites. The reference teaches that histamine release can occur in the lungs, but only when challenged with mosquito extract. Thus, Horsmanheimo et al. is limited to a reaction related to mosquito saliva, and does not speak so broadly to other allergic reactions. In fact, in the only instance in which Horsmanheimo et al. discuss another allergic condition (sensitization with cow allergen), they remark that the

physiological reaction to cow allergen was "somewhat different" than the reaction to mosquito bites. Therefore, not only do Horsmanheimo et al. fail to correlate their findings to other allergic conditions, they demonstrate that their findings are not necessarily applicable to other types of allergic reactions. From this, it can only be ascertained that they fail to teach or suggest all of the claim limitations.

For the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the rejection to claims 41, 62 and 88 under 35 U.S.C. §103(a).

Rejection of claims 53, 72 and 80 under 35 U.S.C. §103(a)

The Examiner has rejected claims 53, 72 and 80 pursuant to 35 U.S.C. §103(a) as being unpatentable over Horsmanheimo et al. in view of Wright et al. and in further view of Stratagene. The Examiner is of the opinion that Horsmanheimo et al. and Wright et al. render the present invention obvious, but fail to teach the use of a kit in a method of treatment. The Examiner contends that the Stratagene catalog teaches a motivation to combine reagents to use in a kit, and that it would have been *prima facie* obvious for one of skill in the art to combine the anti-histamine antibodies taught by Horsmanheimo et al. in view of Wright et al. into a kit as taught by Stratagene, and that the motivation for combining to lessen waste of reagents and for quality control.

The failings of Horsmanheimo et al. in view of Wright et al. have been discussed above and need not be repeated save this brief summary. Horsmanheimo et al. provide no motivation to combine the references to arrive at the present invention because Horsmanheimo et al. teach a non-antibody compound that can be used to treat the histamine and LTC_4 reactions involved in mosquito bites. Thus, the skilled artisan would not be motivated to look to Wright et al. in order to find a suggestion to use an anti-histamine antibody to treat allergy because Horsmanheimo et al. teach that another alternative (cetirizine) already exists. The skilled artisan would not find a reasonable expectation of success in the combined teachings because Horsmanheimo et al. teach that LTC_4 may be the more important mediator of mosquito bite induced wheals and the skilled artisan would not find any reasonable expectation of success in administering an anti-histamine antibody without an anti-LTC_4 antagonist. Similarly, Horsmanheimo et al. in view of Wright et al. fail to teach or suggest all of the claim limitations

because Horsmanheimo et al. only teach the physiological reaction due to mosquito bites, and specifically teach that their results are not common to all allergies.

Stratagene in unable to correct the multiple inadequacies in the teachings of Horsmanheimo et al. in view of Wright et al. Stratagene teaches gene characterization kits, and the present invention is directed to a kit for treating an allergy. There is no reason to apply the teachings of Stratagene to arrive at the present invention because they offer no suggestion or motivation that their kits can be used to treat a mammal, but rather are limited to gene characterization, specifically mapping, sequencing, transcribing, translating, capping or hybridizing nucleic acids. One of skill in the art would not find a suggestion or motivation to assemble a kit for treating an allergy in a mammal wherein the kit comprises an anti-histamine antibody in a reference that solely describes *in vitro* nucleic acid manipulation compositions.

The Stratagene reference also fails to teach or suggest all of the claim limitations. Horsmanheimo et al. do not teach anti-histamine antibodies, and Wright et al. do not correct this defect. There is no mention whatsoever of anti-histamine antibodies in Stratagene, no mention of an applicator, and no mention of a pharmaceutically acceptable carrier. Thereby, because Horsmanheimo et al. in view of Wright et al. in further view of Stratagene do not teach or suggest all of the claim limitations, the references fail the criteria set forth by the Federal Circuit, and do not render the present invention obvious.

Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection of claims 53, 72 and 80 under 35 U.S.C. §103(a).

Rejection of claims 45, 64 and 89 under 35 U.S.C. §103(a)

The Examiner has rejected claims 45, 64 and 89 under 35 U.S.C. §103(a) as being unpatentable over Horsmanheimo et al. in view of Wright et al. and further in view of Snapper (1981, Cytokine Regulation of Humoral Immunity: Basic and Clinical Aspects, pages 325-345). The Examiner states that Horsmanheimo et al. and Wright et al. fail to disclose administering interferon gamma together with an anti-histamine antibody in a method to treat allergy, but that Snapper teaches that administration of interferon gamma induces class switching from Th1 to Th2 type immune responses, and that interferon gamma inhibits IgE secretion by human peripheral blood mononuclear cells cultured with IL-4, thus indicating a role of gamma interferon in IgE responses to allergy. The Examiner contends that it would have been *prima*

facie obvious for one of skill in the art to administer interferon gamma with anti-histamine antibodies, and that an expectation of success because Snapper teaches that interferon gamma inhibits IgE secretion.

Contrary to the Examiner's arguments, Snapper does not offer a reasonable expectation of success in treating allergy of IgE mediated disease. In fact, Snapper directly contradicts the idea of using interferon gamma to treat IgE mediated diseases. Snapper states, "The clinical use of IFN-γ for treatment of IgE-mediated diseases has had limited utility" (page 333, last paragraph). Snapper continues by stating that treating patients with atopic dermatitis, which is well known in the art as a skin disease closely associated with allergies, with interferon gamma failed to consistently lower serum IgE levels. Further, Snapper states that while gamma interferon suppressed *in vivo* and *in vitro* IgE production by B cells in patients afflicted with hyper IgE syndrome, treatment with IgE did not lead to a significant clinical improvement.

Thus, not only does Snapper fail to provide a reasonable expectation of success, the disclosure actually teaches away from using gamma interferon as a part of a treatment for allergies and IgE related conditions. By highlighting the failures of interferon gamma therapy, Snapper fails to provide the skilled artisan with a reasonable expectation of success or a motivation to combine Snapper with Horsmanheimo et al. and Wright et al., which as discussed above, fail to teach an anti-histamine antibody.

For the reasons set forth above, Applicants submit that Horsmanheimo et al. in view of Wright et al. and in further view of Snapper fail to render the present invention obvious and reconsideration and withdrawal of the rejection of claims 45, 64 and 89 under 35 U.S.C. §103(a) is respectfully requested at this time.

Rejection of claims 54, 73 and 81 under 35 U.S.C. §103(a)

The Examiner has rejected claims 54, 73 and 81 under 35 U.S.C. §103(a) as being unpatentable over Horsmanheimo et al. in view of Wright et al. and Stratagene and in further view of Snapper. The Examiner states that it would have been prima facie obvious to one of ordinary skill in the art to combine anti-histamine antibodies with gamma interferon into a kit for the treatment of allergies.

As stated above, Horsmanheimo et al. teach a non-antibody compound that can be used to treat the histamine and LTC_4 reactions involved in mosquito bites and therefore the

skilled artisan would not find a suggestion to use an anti-histamine antibody to treat allergies in a mammal. Further, the skilled artisan would not find any reasonable expectation of success in administering an anti-histamine antibody without an anti-LTC_4 antagonist. In addition, Horsmanheimo et al. in view of Wright et al. fail to teach or suggest all of the claim limitations because Horsmanheimo et al. specifically teach that their results are not common to all allergies. Snapper fails to rectify the lack of teaching in Horsmanheimo et al. and Wright et al. because Snapper teaches that interferon gamma has limited clinical utility and actually teaches away from administering interferon gamma in IgE related and allergic disease.

The Stratagene reference does not correct the defects in the three above-identified references because Stratagene fails to teach or suggest all of the claim limitations. Specifically, Stratagene does not disclose anti-histamine antibodies, an applicator, or a pharmaceutically acceptable carrier. Therefore, because Horsmanheimo et al. in view of Wright et al. in further view of Stratagene do not teach or suggest all of the claim limitations, the references fail to render the present invention obvious.

In addition, Stratagene further fails to correct the defects in Horsmanheimo et al., Wright et al. and Snapper because the reference provides a motivation solely related to improving economy and decreasing waste and clutter in the molecular biology laboratory. None of the stated goals of the Stratagene kit format provide an analogous goal in the treatment of allergy in a mammal. The disparities between a kit for treating a disease and a kit for *in vitro* express translation of a protein are too great for the requisite motivation to combine references to exist and therefore, does not render the present invention obvious.

For the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 54, 73 and 81 under 35 U.S.C. §103(a).

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome, and that claims 41, 45, 53, 54, 62, 64, 72, 73, 80, 81, 88 and 89 are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

Boris Skurkovich et al.

April 7, 2004
(Date)

By: Kathryn Doyle

KATHRYN DOYLE, Ph.D, J.D.
Registration No. 36,317
MORGAN, LEWIS & BOCKIUS, LLP
1701 Market Street
Philadelphia, PA 19103-2921
Telephone: (215) 963-5000
Direct Dial: (215) 963-4723
Facsimile: (215) 963-5001
E-Mail: kdoyle@morganlewis.com
Attorney for Applicants

KD/JDGB

Enclosures: Copy of Supplemental IDS filed September 26, 2002